Statistical Analysis Plan

COVID-19 Associated Acute Kidney Injury: Long Term Outcomes

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Abstract

This prospective analysis of retrospectively collected data as detailed within the EthICAL study will focus on the long-term renal function and mortality associated with acute kidney injury within COVID-19 patients admitted to five acute hospitals within East London during the pandemic. It will also examine the incidence, risk factors, and outcomes associated with acute kidney injury within COVID-19 patients admitted to five acute hospitals within East London during the second wave of the pandemic.

Introduction

COVID-19 associated acute kidney injury (COVID-AKI) is highly prevalent. Notwithstanding changing pathophysiology, prevalence, and outcomes observed throughout the pandemic[1], it is estimated that one in ten COVID-19 patients treated on medical wards and one half of COVID-19 patients admitted to the intensive care unit (ICU) experience concomitant acute kidney injury (AKI) (REF). Of those admitted to the ICU with COVID-AKI half require renal replacement therapy (RRT)[2-5], Older age[6-8], socioeconomic status[9], the need for respiratory support or mechanical ventilation[7], previous prescription of nephrotoxic medication, higher baseline creatinine[6-9], higher CRP[9], physiological derangement[7,8], and additional comorbidities including but not limited to diabetes, heart disease, and hypertension are all associated with increased risk[9,10]. Ethnicity also not only increases one's risk of developing COVID-AKI, but also moderates the consequent trajectory of the disease[9].

COVID-AKI is associated with poor clinical outcome. Those with COVID-AKI experience a 2-3x increase in mortality[10,11], with greater AKI severity pertaining to increased mortality risk[12]. For ICU COVID-AKI patients outcomes are even worse. Early studies reported up to 75% mortality in this cohort of patients[13,14] albeit with significant variation reported between centres[15,16].

Despite a relatively comprehensive albeit heterogenous evidence base reporting the prevalence and short to medium term outcomes of COVID-AKI, there is limited understanding regarding the longer-term prognosis and renal outcomes in this cohort of patients. Studies are few, small, and limited in duration of follow-up. In a relatively small cohort study of 313 COVID-AKI patients, Lumlertgul et al.[5] reported 90% renal recovery at 90 days, in keeping with follow-up data in a larger cohort of ICU patients[1]. A cohort of 12,891 hospitalised patients[17] experienced median time to renal recovery (<125% baseline) of 13 days for KDIGO stage I and 34 days for KDIGO stage II. 42.9%, 51%, and 69.8% of those with KDIGO stages I, II, and III respectively experienced renal non-recovery. Age, male sex, and hypertension all appear to moderate risk of renal non-recovery[17]. Those receiving RRT have comparable rates of renal non-recovery to all KDIGO stage III COVID-AKI patients[12] although again there remains significant

heterogeneity in patient population and outcomes reported within the literature[18,19]. It is likely the prevalence of longer-term renal dysfunction and renal non-recovery is likely higher than reported, given the observed loss in muscle mass mitigating potential reduced creatinine clearance in this cohort of patients[9].

Crucially, our understanding regarding COVID-AKI is primarily derived from data collected during the first wave of the pandemic. In truth the only comprehensive study comparing the characteristics of COVID-AKI patients between waves presents data from a single critical care unit in London, and describes significant difference in the characteristics, incidence, and outcomes of COVID-AKI in this cohort patients[1]. Our group has previously shown that in a cohort of wave 1 patients from five centres in London that numerous demographic, sociological, pathological, and biochemical variables predict COVID-AKI, that outcomes differ both dependent on these characteristics and severity of COVID-AKI, and that the trajectory of COVID-AKI differs between cohorts[9]. Those with persistent AKI are also at significantly increased risk of mortality, with an odds ratio of 7.57 at 90 days. Given the disparity in outcomes reported across the evidence base, and the lack of understanding of long-term outcomes of COVID-AKI patients, we now want to compare the characteristics and outcomes of this cohort of patients with those admitted during the second wave, whilst also evaluating the long-term outcomes of both cohorts of patients. We will attempt to address this knowledge gap by performing a prospective analysis of long-term renal function and patient mortality in COVID-AKI patients admitted to five acute hospitals in East London between 1st January 2020 and 13th May 2020 (wave 1) and between 1st September 2020 and 17th February 2021 (wave 2). We will also report outcomes for the cohort of patients admitted with COVID-19 over the same period who did not subsequently experience COVID-AKI. In doing so we will further evaluate risk factors and moderators of adverse outcomes, including but not limited to ethnicity and demographic variables, comorbid conditions, and a number of inpatient clinical and biochemical markers of severity of both COVID-AKI.

Hypothesis

In keeping with the current evidence base we anticipate that the majority of COVID-19 related AKI patients experience renal recovery by 90 days. However, we predict that a subgroup of patients will experience persistent renal dysfunction, with this relationship moderated by age, severity of inpatient AKI, persistence of inpatient AKI, and comorbidities including but not limited to hypertension, diabetes mellitus, and chronic kidney disease diagnosed prior to admission with COVID-19. We anticipate that those with severe or persistent inpatient AKI also experience higher Major Adverse Kidney Event (MAKE) outcomes with a subset of this cohort experiencing apparent recovery followed by a delayed decline in renal function.

Study objectives and outcomes

Primary objective

To quantify rates of MAKE outcomes at 365 days (MAKE-365) post-AKI in COVID-AKI patients admitted to the identified centres during the COVID-19 pandemic.

Secondary objectives

To quantify MAKE outcomes at the identified intervals up to 3 years post-AKI in in COVID-AKI patients admitted to the identified centres during the COVID-19 pandemic.

To examine if there are differences in prevalence and trajectories of AKI categorised by severity and patterns of recovery between pandemic waves.

To determine risk factors for developing the aforementioned outcomes.

Outcome measures

Primary Outcome

Composite MAKE 365 outcome where follow-up data is available. All data also presented as components of composite outcome (see Table 2).

- Death
- New requirement for dialysis
- Worsened renal function defined as eGFR <70% of baseline

Secondary Outcomes

Renal non-recovery (serum creatinine >150% baseline):

- 90 days

Composite MAKE outcome at day 30, 90, 180, 730 where follow-up data is available. All data also presented as components of composite outcome (see Table 2).

- Death
- New requirement for dialysis
- Worsened renal function defined as eGFR <70% of baseline

Additional exploratory analysis as detailed below including multiple regression analysis of risk factors of aforementioned adverse kidney events and overall survival.

Methods

We will undertake a prospective cohort study using retrospectively collected data as reported in the EthICAL study on ethnic disparities in COVID-19 outcomes[20]. This will include all patients with confirmed COVID-19 infection admitted to the five acute hospitals within Barts Health NHS Trust between 1st January 2020 and 13th May 2020 (wave 1) and between 1st September 2020 and 17th February 2021 (wave 2). Details of data collection, data management and permissions are detailed in the EthICAL study documents. STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines will be followed and reported.

Data Analysis

Definition of key variables

Baseline Creatinine

Baseline creatinine will be set using the median result from all blood tests 7-365 days prior to admission. If no prior results are available, baseline creatinine will be imputed based on an estimated glomerular filtration rate (eGFR) of 75 mL/min/1.72 m2 or admission creatinine, whichever is lower.

Acute Kidney injury

Acute Kidney Injury (AKI) is defined according to KDIGO criteria[21]. The median creatinine value in the 7-365 days prior to admission will be used as baseline value. If no prior results are available, value will be imputed based on eGFR of 75ml/min/1.72m[22] or the admission value, whichever is lower.

Any rise in creatinine meeting criteria within the first 7 days of admission with be classified as AKI. Patients with AKI will be stratified into three groups based on severity: Stage 1 (peak creatinine 1.5-1.9 times baseline or 3 26.5 µmol/L increase in 48h); Stage 2 (peak creatinine 2.0-2.9 times baseline); and Stage 3 (peak creatinine 3 times baseline; 3 26µmol/L increase to a value of 353.6 µmol/L or higher; or initiation of RRT).

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline or ≥0.3 mg/dl (≥26.5 µmol/l) increase	<0.5 ml/kg/h for 6–12 h
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ≥12 h
3	3 times baseline or ≥4.0 mg/dl (≥353.6 µmol/l) increase or initiation of RRT or in patients <18 years a decrease in eGFR <35 ml/min/1.73 m^2	<0.3 ml/kg/h for ≥24 h or anuria ≥12 h

Table 1: KDIGO criteria for diagnosis of Acute Kidney Injury[21]. In this analysis, only biochemical criteria will be used as there is no data regarding urine outputs is available.

Renal non-recovery

Renal non-recovery was defined as serum creatinine >150% baseline or dialysis independence at 90-day follow-up.

Comorbidity and Hospital Frailty Risk score

ICD-10 codes for all previous hospital encounters up to the current admission will be used to identify significant pre-admission co-morbidities. Cumulative Charlson comorbidity index[24] and Hospital Frailty Risk Score will be calculated using this information[25].

Body mass index (BMI)

BMI will be calculated using weight and height taken at current or (if unavailable) penultimate admission episode.

Chronic Kidney Disease (CKD)

Cases of moderate-to-severe CKD will be defined as three or more months of eGFR of <60 mL/min/1.73m2, corresponding to moderate-to-severe CKD based on 2005 KDIGO classification[26].

Stage	Description	Classification by severity: GFR mL/min/1.73 m^2	Classification by severity: Related terms	Classification by treatment
1	Kidney damage with normal or ↑ GFR	≥90	Albuminuria, proteinuria, hematuria	
2	Kidney damage with mild ↓ GFR	60–89	Albuminuria, proteinuria, hematuria	
3	Moderate ↓ GFR	30–59	Chronic renal insufficiency, early renal insufficiency	T if kidney transplant recipient
4	Severe ↓ GFR	15–29	Chronic renal insufficiency, late renal insufficiency, pre-ESRD	
5	Kidney failure	<15 (or dialysis)	Renal failure, uremia, end-stage renal disease	
				D if dialysis (hemodialysis, peritoneal dialysis)

Abbreviations are: GFR, glomerular filtration rate; ESRD, end-stage renal disease.
Related terms for CKD stages 3 to 5 do not have specific definitions, except ESRD.

Table 2: KDIGO classification of Chronic Kidney Disease[26].

Mortality

Up to date information regarding death was extracted on 24th November 2022. Death is defined as the presence of date of death or "patient died" as discharge destination in the EMR database (synchronised with NHS Spine to capture out of hospital deaths).

Software

Data will be stored in Microsoft Excel (2022; version 16.69) and analysed using R software (R core team; 2022)

Statistical Analysis

Baseline characteristics

Baseline characteristics for COVID-AKI patients with and without AKI will be summarised for wave 2 participants. AKI will be categorised by stage. Numbers (%), means (SD), and medians (IQR) will be provided separately. For wave 2, as per Wan et al.[9], between group proportions (AKI vs. No AKI) will be compared using Pearson's chi-square or Fisher's exact test and continuous variables using a two-sample t-test or Wilcoxon rank-sum or signed rank tests as appropriate. Multivariable logistic regression will be carried out to assess risk factors for development of AKI for wave 2 participants only. We will describe similarities and comparisons in patient characteristics between wave 1 and wave 2 patients who developed AKI.

	All	No AKI	AKI	AKI Stage 1	AKI Stage 2	AKI Stage 3	P value
N							
Age (years) Median (IQR)							
Male (%)							
Ethnic group (Asian or Asian British; Black or Black British; Mixed and Other; Unknown; White)							
IMD quintile (1 = most deprived; 2; 3; 4; 5 = least deprived)							
Smoking							
BMI							
Hospital Frailty Risk Score							
Rockwood Frailty Score (1-2; 3-4; 5-6; 8-9)							
Charlson Co-morbidity Index (0; 1-2; 3-4; >=≥5)							
HFRS (<5; 5-15; ≥15)							
MI							
CHF							
CVD							
PVD							
Hypertension							
Dementia							
COPD							
Rheum disease							
Peptic ulcer							
Liver disease							
DM							
Premorbid CKD							
ESRD							
eGFR (baseline median; <60; last median; >60)							
Baseline creatinine							
Peak CRP							
Malignancy							
ICU admission							
ICU LoS							
Hospital LoS							
Total number organ systems affected							
RRT							
Mechanical ventilation							
Discharge destination (Care home or equivalent; health-related institution; usual place of residence; hospice or equivalent; temporary place of residence)							

Sample Table 1: The assessment of risk factors and outcomes associated with AKI amongst COVID-19 patients

Comparison of clinical outcomes

Multivariable logistic regression will be carried out to assess for risk factors for development of COVID-AKI, and survival, in wave 2. Results will be presented in the form of Forest plots.

Kaplan-Meier curves with be calculated and between group comparison will be performed using log-rank test. Cox-proportional hazard models will be used to determine difference in renal non-recovery, subsequent CKD diagnosis, and MAKE endpoints between groups, as well as to assess survival adjusted for age and sex, with a further multivariable model to assess effect of risk factors associated with worse outcomes as described within our previous paper[9].

Logistic and linear regression models will be used to assess the between-group differences for additional categorical and continuous secondary outcomes.

	All Wave 1	All Wave 2	Wave 1					Wave 2					P value
			No AKI	AKI	AKI Stage 1	AKI Stage 2	AKI Stage 3	No AKI	AKI	AKI Stage 1	AKI Stage 2	AKI Stage 3	
Renal non-recovery at 90 days													
Died													
Days to death Median													
Died within 30 days													
Died within 90 days													
MAKE 30													
MAKE 90													
MAKE 180													
MAKE 365													
MAKE 730													
New (persistent) requirement for dialysis													
Final eGFR <70% baseline													

Sample Table 2: Outcomes associated with AKI amongst COVID-19 patients

Analysis of COVID-AKI Trajectories and Sensitivity Analysis

Baseline, first, peak, and last creatinine pre-discharge as well as on day 30, 90, 180, 365, and 730 will be presented as descriptive data only for each of the aforementioned groups.

Multivariable logistic regression will then be performed for patients with recovered, relapsed, and persistent AKI for both wave 1 and 2 to assess for risk factors for the aforementioned outcomes.

Secondary analysis of outcomes will be carried out for the following groups:

- **Late AKI** – patients who only developed AKI after day 7 of admission
- **Persistent AKI** – patients whose AKI persisted at day 7, including those who died before day 7 and all RRT patients
- **Recovered AKI** – patients no longer meeting criteria for AKI at day 7 or at any later point during the admission
- **Relapsed AKI** – patients recovered at day 7 who met criteria for AKI again at a later point during the admission

- **End-stage renal failure/dialysis dependence**

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